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Dr. Samuel H. Wilson
Acting Director
National Institute of Environmental Health Sciences
and National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Wilson:

The Styrene Information and Research Center[1] is writing to ask that you postpone the meeting of the National Toxicology Program's (NTP's) *Report on Carcinogens* (*RoC*) Expert Panel on styrene, scheduled for July 21-22, 2008. This meeting was announced when the NTP's Draft Background Document for Styrene was noticed in the May 20, 2008, *Federal Register*.

The draft document on styrene should not be reviewed by the Expert Panel at this time. To proceed to Expert Panel review with the current draft would deny the panel an opportunity to review completely the critical science with a full understanding of the interpretative issues raised in the current draft. Proceeding as announced also would prevent NTP from realizing the value of its expert-panel-based scientific review. While we realize that this is an unusual procedural request, our justification for making it is provided below.

As you are aware, the revised process for NTP's *12th Report on Carcinogens* specifies that an Expert Panel appointed by NTP review a draft background document and then make a recommendation for listing in the *Report on Carcinogens* and provide the scientific justification for that recommendation. The NTP staff itself does not recommend a specific listing decision on the subject chemical. Therefore, the Expert

[1] The Styrene Information and Research Center's (SIRC's) mission is to evaluate existing data on potential health effects of styrene, and develop additional data where it is needed. SIRC has gained recognition as a reliable source of information on styrene and helping ensure that regulatory decisions are based on sound science. For more information, visit http://www.styrene.org.

Panel's recommendation represents the initial determination for a chemical. Under the NTP process, this determination is to flow from the Panel's review of the draft background document on the chemical. For that reason, the process requires that the background document be complete with regard to the discussion of the key scientific studies and analysis that bear directly on the determination of whether or not a chemical may be a carcinogen. We believe that NTP's styrene background document is far from complete and is not ready for review by the Expert Panel for the following reasons:

Human Studies

We were very surprised that the NTP draft document on styrene relies heavily on the 2002 International Agency for Research on Cancer's (IARC's) review of the epidemiology data, which is now out of date. The IARC review was based primarily on studies of composite industry workers by Kolstad and co-workers (Kolstad et al., 1993, 1994, 1995, 1996), where the only statistically significant finding was with regard to workers who had worked for one year or less. IARC discounted the Okun et al., 1985 study of 5,000 composite workers primarily due to the lack of adequate follow up and small size. However, since the IARC meeting Okun has been updated by Ruder et al., 2004 with 20 years of follow-up data, and shows no indication of the leukemia that was of concern to the IARC panel.

In addition, the author of the epidemiology section of NTP's background document on styrene was Dr. Kolstad himself. Significant deficiencies in the Kolstad study have been identified and were included in the documents SIRC submitted to NTP at the beginning of its styrene review process. For example, the background document talks about "probable high exposure" and "probable low exposure" groups, but the Kolstad study only identified whether employees worked in companies where more or less than 50% of the workers were thought by one source to work in reinforced plastics, not whether their exposure within the company was high or low. There was serious disagreement about this between company owners and resin supply dealers. However, these deficiencies were not mentioned in the draft document.

We are sure that NTP is aware of the need to avoid even the appearance of a conflict of interest on the part of its contractors who are preparing these key scientific documents for review by expert panels. We believe that this standard was not met in this instance, and that therefore the treatment of the Kolstad paper in the draft background document needs to be adjusted accordingly before it is reviewed by the Expert Panel.

Furthermore, additional studies on the Styrene-Butadiene-Rubber (SBR) cohort extensively described in the draft background document have been published by Delzell and co-workers (Sathiakumar et al., 2005; Macaluso, et al., 2004; and Graff et al., 2005) that show that styrene was not likely to be the causative factor in the original study. Instead, these further studies focus the concerns on other chemicals also present in the

workplace including dimethyldithiocarbamate (DMDTC) and 1,3-butadiene. While these critical composites industry and SBR worker study updates are listed as references in the draft NTP background document, the author emphasized associations with styrene and not with other chemicals in characterizing the epidemiological data.

For all the reasons given above, the draft background document fails to provide a reasonably accurate, complete, and up-to-date assessment of the important epidemiological data, and cannot serve as an adequate basis for the panel's review.

Given the recent availability of these updates to the critical epidemiological studies, we are accelerating our plans to convene a special independent blue ribbon epidemiology panel to review the current state of the epidemiological science on styrene. The panel will submit this review to NTP staff for its review at the same time it is submitted to SIRC. We had been discussing convening such a panel in order to provide an update on the epidemiology to IARC in preparation for any future IARC review of styrene. It is now clear that such a Panel is essential to the NTP process and should be completed as soon as possible. We believe that a comprehensive review of the current epidemiological data to date will show that the “limited evidence” finding of the IARC panel on which the NTP draft relies so heavily is not current and cannot be justified.

Mode of Action

We also believe that the draft *RoC* document on styrene has some fundamental flaws in its section on cancer. The NTP consultant addressed some potential modes of action for the formation of mouse lung tumors from styrene exposure. However, the document relied almost exclusively on the conclusions of the Harvard Panel (Cohen et al., 2002) regarding styrene oxide-related cytotoxicity. A proposed mode of action involving mouse-lung- specific metabolism by CYP2F2 was published shortly after the Harvard Panel (Cruzan et al., 2002). Additional research since 2002 has further supported this mode of action. Although all the studies relevant to this mode are presented and discussed in the section of the document on lung toxicity, this proposed mode of action is not discussed in the cancer section. We believe a discussion of this hypothesis must be part of the evaluation of the human relevance for mouse lung tumors.

If the Expert Panel were to conclude that the data that showed mouse lung tumors associated with exposure to styrene are not relevant to human carcinogenicity (as we believe the omitted data show), then the Expert Panel would have a strong basis for concluding that styrene should NOT be listed in the Report on Carcinogens. This ultimately is a decision for the Expert Panel at this stage in the NTP process, but how can the Expert Panel be reasonably expected to consider this possibility if the underlying data are not part of the mode of action section of the background document?

We believe that these fundamental interpretation issues on epidemiology and mode of action are not well-suited to the kind of short, two-day expert panel meeting that the NTP has scheduled for July, but instead should be addressed first by a specialized blue ribbon panel (in the case of the epidemiology data), and then by the NTP staff and consultants and reflected in an appropriate manner in the discussion contained in the styrene background document provided to the Expert Panel for its review. With a complete and accurate report in hand, the Expert Panel would then be in a position to peer review the document and render their recommendation on the listing decision for styrene.

It is not possible for us to arrange for an independent blue ribbon panel of epidemiologists in the short time frame between the *Federal Register* notice of May 20 and the scheduled meeting dates of July 21-22. Accordingly, we request a postponement of the Expert Panel meeting until this blue ribbon panel report, and its findings, can be reviewed and potentially incorporated, together with changes in the cancer section as discussed above, into the material to be reviewed by the Expert Panel. Although this postponement might appear to delay the process, we believe that providing the Expert Panel a more accurate, complete, and up-to-date draft to review at this initial stage will avoid major corrections in the document later in the process and possible re-reviews and other delays.

Because the contract for the blue ribbon panel has not yet been negotiated, we are unable at this point in time determine when the panel will send its report to NTP. However, it is our current hope that the Panel could complete its report within 3-4 months. As soon as the timing is clear, we will inform you by means of a supplemental letter. In addition, because the panel has not yet been established, we would be happy to discuss with your staff the membership of the panel and how it should conduct its review.

We look forward to, and appreciate, your response.

Very truly yours,

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cc: Dr. Ruth M. Lunn, NTP